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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,196	01/12/2007	Madeleine M. Joullie	1694.0610001	8339

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
12/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,196	JOULLIE, MADELEINE M.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,14,16,17,19,21,27 and 34* is/are rejected.

7)☒ Claim(s) *3,8,24,30 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/20/2010 and 09/20/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

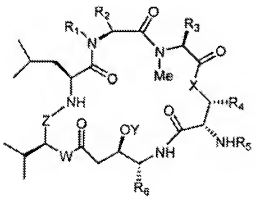
Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-7,9,11-13,15,18,20,22,23,25,26,28,29,32,33 and 35-39.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, drawn to a product, in the reply filed on 9/202/2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

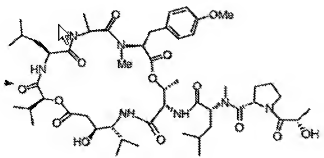
Applicant's election of the species compound 75 [N-Ala4]-Tamandarin B



I

which is the compound of formula I wherein R1 is H, R2 is CH3, R3 is 4-methoxybenzyl, R4 is CH3, R5 is N-methyl-R-leucine-S-proline-S-lactate, R6 is valine side chain, X is O and Y is H (see page 48, lines 4-6 of the application as filed) in the reply filed on 9/20/2010 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Examiner further emphasizes that this is an election of species and not a restriction requirement and therefore if a species is found allowable the search will be expanded accordingly.

Thus the elected species was:



75

Compound 75

Status of the claims

2. Claims 1-39 are pending in the application. Claims 4-7, 9, 11-13, 15, 18, 20, 22-23, 25-26, 28-29, 32-33 are withdrawn as not drawn to the elected species, claims 35-39 are withdrawn as not drawn to the elected group. Claims 1-3, 8, 10, 14, 16-17, 19, 21, 24, 27, 30, 31 and 34 are presented for examination on the merits.

The species compound 75 was searched and found free of the prior art (see claim objections below). The search was expanded by Examiner and two new species were found and which are herein both examined for the sake of compact prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (J Peptide Res, 1999, cited in the IDS of 9/20/2010).

Schmidt et al. disclose a compound encompassed by Formula I. See, e.g. compound 47 in Table of page 149, notation referring to Figure 1, page 147, except that it does not teach the specific stereochemistry claimed. Please note that, with respect to the instantly claimed formula 3, the compound has R4 equals H and therefore the proviso at the end of the claim 1 does not apply. Z is CO-CH(CH3)-CO. The compound belongs to the highly cytostatic didemnins containing a 23-membered cyclopeptolide with a side chain attached to the backbone through the amine group of threonine. The compounds with D-MeLeu (R5 in the compound of formula I, reading upon an amino acid residue) attached to threonine show remarkable biological activities.

What is missing in Schmidt et al. is the specific stereochemistry of Formula I.

However Schmidt et al. do teach changing the stereochemistry of the residues (e.g., page 147) and that, for example, in order to obtain potent cancerostatic activity,

the presence of D-MeLeu is essential, in the case of didemnin B, its replacement by L-MeLeu results in an appreciable decrease in activity. Also diastereomer 35 reveals no decrease in activity in comparison with the highly active didemnin B (2).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the compounds of Schmidt et al. to obtain other stereoisomers. One of ordinary skill in the art at the time the invention was made would have been motivated to do so in order to determine high activity stereoisomers from those of lower or no activity. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since such modifications were known in the art and were achievable via changes in the stereochemistry of the reagents used to obtain the final compounds.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joullie et al. (WO 01/76616, cited in the IDS of 9/20/2010) in view of Bren (J Peptide Res, 1999).

Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of

using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as enhancers of apoptosis are also provided. Joullie et al teach a compound of formula I wherein R3 can be a fluorophore (e.g., pages 1-25, Figures 27-28, 32-40).

Joullie et al. do not expressly teach the fluorophore being "naphthylmethyl".

Bren discloses organic fluorophores including, e.g., those containing naphthylmethyl as fluorophores (e.g., pages 1022 and 1027).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace, e.g., the residue corresponding to R2 for a fluorophore (see, e.g., pages 2-3, Figures e.g., 27-28 and 32-40) such as naphthylmethyl. One of ordinary skill in the art would have been motivated to do so because Joullie et al. teach such modifications (see, e.g., pages 2-3) and because Bren teaches that naphthylmethyl is a fluorophore (e.g., pages 1022 and 1027). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since synthetically such kind of modifications can be achieved by changing reagents and conditions. Furthermore, modifications of stereochemistry are also taught by Joullie et al. including varying the stereochemistry of the proline or lactate moieity (S) vs. (R), and such synthetic variations (e.g., pages 38-50).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Objections

6. Claims 3, 8, 24, 30, 31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 of U.S. Patent No. 6,509,315, cited in IDS dated 9/20/2010, in view of Bren (J Peptide Res, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to compounds of Formula I. Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as enhancers of apoptosis are also provided. Joullie et al teach a compound of formula I wherein R3 can be a fluorophore (e.g., claims).

Joullie et al. do not expressly teach the fluorophore being "naphthylmethyl".

Bren discloses organic fluorophores including, e.g., those containing naphthylmethyl as fluorophores (e.g., pages 1022 and 1027).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace, e.g., the residue corresponding to R2 for a fluorophore (see, e.g., claim 1) such as naphthylmethyl. One of ordinary skill in the art would have

been motivated to do so because Joullie et al. teach such modifications (see, e.g., pages 2-3) and because Bren teaches that naphthylmethyl is a fluorophore (e.g., pages 1022 and 1027). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since synthetically such kind of modifications can be achieved by changing reagents and conditions. Furthermore, modifications of stereochemistry are also taught by Joullie et al. including varying the stereochemistry of the proline or lactate moieity (S) vs. (R), and such synthetic variations (e.g., claims).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 7,064,105, cited in IDS dated 9/20/2010, in view of Bren (J Peptide Res, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to compounds of Formula I. Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as

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10. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 7,122,159, cited in IDS dated 9/20/2010, in view of Bren (J Peptide Res, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to compounds of Formula I. Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as enhancers of apoptosis are also provided. Joullie et al teach a compound of formula I wherein R3 can be a fluorophore (e.g., claims).

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modifications of stereochemistry are also taught by Joullie et al. including varying the stereochemistry of the proline or lactate moieity (S) vs. (R), and such synthetic variations (e.g., claims).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 7,651,997, cited in IDS 9/20/2010, in view of Bren (J Peptide Res, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to compounds of Formula I. Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as enhancers of apoptosis are also provided. Joullie et al teach a compound of formula I wherein R3 can be a fluorophore (e.g., claims).

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12. Claims 1-2, 10, 14, 16, 17, 19, 21, 27, 34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 7,737,114 in view of Bren (J Peptide Res, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to compounds of Formula I. Joullie et al. teach didemnin and tamandarin analogs which have a deoxo-proline residue or a dehydro-proline

residue in their structure. These analogs are useful as anti-cancer agents and for other purposes. Methods of making the analogs and methods of using them as inhibitors of protein synthesis, cell growth and tumorigenesis and as enhancers of apoptosis are also provided. Joullie et al teach a compound of formula I wherein R3 can be a fluorophore (e.g., claims).

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ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

13. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/

Examiner, Art Unit 1654

MMCG 11/2010